THE FRAMINGHAM STUDY

Data and Materials Distribution Agreement Form

The undersigned parties hereby enter into this Distribution Agreement as of the date specified on the final page hereof.

PRELIMINARY STATEMENT

The National Heart, Lung, and Blood Institute (NHLBI), in collaboration with Boston University, has supported collection of blood samples and clinical data from participants in the Framingham Heart Study since 1948. This clinically and genetically well characterized population provides a rare and valuable scientific resource maintained under the joint stewardship of Boston University and the NHLBI. Promoting optimal use on a national scale of such a resource will require a large and concerted effort which may exceed the research capacity of currently available investigators in Framingham and other individual study locations. The NHLBI and the researchers it supports have a responsibility to the public in general, and to the scientific community in particular, to encourage as rapid scientific progress as possible using these resources, subject to appropriate terms and conditions. In order to take full advantage of such resources and maximize their research value, it is important that samples and data collected with public funds be made available, on appropriate terms and conditions, to the largest possible number of qualified investigators in timely manner.

Blood samples and clinical data collected by the Framingham Heart Study have been stripped of all personal identifiers but the confined nature of the geographic area from which these subjects were drawn and the wealth of data available on them in publicly available records would make less difficult the individual identification of some subjects. To protect the confidentiality and privacy of these participants and their families, investigators granted access to these data and materials must adhere to the requirements of this Distribution Agreement. Failure to comply with this Distribution Agreement could result in denial of further access to Framingham samples and data. Violation of the confidentiality requirements of this agreement is considered a breach of confidentiality and may leave requesting investigators liable to legal action on the part of Framingham Study participants, their families, or the U. S. Government.

The Framingham investigators (both from Boston University and the NHLBI) have made a substantial long-term contribution in establishing and maintaining the clinical database and the genetic database and samples. The NHLBI and Boston University seek to encourage appropriate collaborative relationships by outside investigators with the Framingham investigators and to ensure that the contribution of the Framingham investigators is appropriately acknowledged.

The NHLBI and Boston University further seek to promote the development of valuable discoveries and inventions beneficial to the public health based upon use of this Framingham Study repository of valuable materials and data.

DEFINITIONS

For purposes of this agreement,

"Clinical Data" refers to data, and associated records, collected and recorded from Framingham Study subjects through the periodic Original Cohort and Offspring Examinations conducted pursuant to Boston University's contract with the NHLBI;

"Biological Materials" refers to blood samples and products thereof including immortalized lymphocytes and extracted DNA collected and prepared pursuant to Boston University's contract with the NHLBI;

"Genetic Analysis Data" refers collectively to "Molecular Genetic Data" and "Linkage Analysis Data" as these terms are defined below;

"Molecular Genetic Data" consists of data derived from analyses of DNA samples contained in Biological Materials including but not limited to genotyping analysis, anonymous marker polymorphisms, DNA sequence information, mutation analysis and other genetic analyses.

"Linkage Analysis Data" consists of data derived from statistical analyses linking Molecular Genetic Data with Clinical Data including but not limited to genetic linkage analysis, transmission disequilibrium analysis, haplotype relative risk analysis and other statistical genetic techniques.

RECIPIENT

_____ , a [non-profit] OR [for-profit] corporation organized under the laws of the State of _____with a principal address at _____ ("Recipient") requests access to Framingham Clinical Data, Genetic Analysis Data and Biological Materials at its sole risk and at no expense to Boston University or NHLBI.

AGREED TERMS AND CONDITIONS

It is mutually agreed as follows:

1. Biological Material. Boston University and NHLBI, agree to transfer to Recipient Biological Materials described below for use by the Recipient's principal investigator named below ("Principal Investigator") to conduct the research described in paragraph 4 below. These Biological Materials (including numbers of samples and whether samples are unique or immortalized) are described as follows:

2. Clinical Data. Boston University and NHLBI, agree to provide Recipient with Clinical Data described as
follows:_____
_____
_____

3. Genetic Analysis Data. Boston University and NHLBI, agree to provide Recipient with

Genetic Analysis Data, if available, described as follows:_____

_____

_____ Boston University will provide Recipient with the name and address of any and all other Investigator(s) who generated such "Genetic Analysis Data."

4. Research Project.

4.1 This Biological Material, Clinical Data and /or Genetic Analysis Data will be used by Recipient's Principal Investigator solely in connection with the following research project ("Research Project"), specifically described below or in an attached Exhibit A:_____

_____

_____

4.2 The Research Project (circle one); [does][does not] involve Boston University investigator(s) as co-investigator(s). If the Project does involve Boston University co-investigator(s), their names are: _____ and the work they will perform is described below or in an attached Exhibit B:_____

_____

_____

4.3 This Distribution Agreement covers only the above-described Research Project. Recipient will submit a completed Distribution Agreement (this document) for each research project for which Clinical Data and Biological Materials are requested.

5. Non-transferability. This Distribution Agreement is not transferable. Recipient agrees that substantive changes made to the Research Project described above, and/or appointment by Recipient of another Principal Investigator to complete the Research Project, require execution of a new Distribution Agreement in which the new Principal Investigator and/or new Research Project are designated.

6. Publication. Prompt publication of the results of the Research Project is encouraged. Recipient agrees to provide to Boston University and NHLBI a copy of any abstract ten (10) days in advance of submission for publication and any manuscript thirty (30) days in advance of submission for publication, in order to permit review and comment and ensure compliance with the confidentiality requirements of this Agreement.

7. Acknowledgments. Recipient agrees to acknowledge the contribution of Boston University and NHLBI Framingham staff in any and all oral and written presentations, disclosures, and publications resulting from any and all analyses of Clinical Data and Biological Materials.

7.1 Collaborations/Acknowledgments. If the Research Project involves a collaboration with Boston University co-investigators (see paragraph 4 above), then Recipients will acknowledge Boston University co-investigators as co-authors, as appropriate, on any publication. In addition, the manuscript will be reviewed by NHLBI and the Recipient will use the first acknowledgment printed below.

7.2 Other Studies/Acknowledgments. If the Research Project does not involve a collaboration with Boston University co-investigators (see paragraph 4 above), then the manuscripts, upon submission pursuant to paragraph 6 above, will be reviewed by Boston University and NHLBI for scientific content and consistency of data interpretation with previous Framingham publications. If Recipient agrees to incorporate significant comments from the review, Recipient will use the acknowledgment printed below. [The process for review of manuscripts by Boston University and NHLBI is described in Attachments 1 and 2, respectively.]

"The Framingham Heart Study is conducted and supported by the National Heart, Lung, and Blood Institute (NHLBI) in collaboration with Boston University. This manuscript has been reviewed by Boston University and NHLBI for scientific content and consistency of data interpretation with previous Framingham publications and significant comments have been incorporated prior to submission for publication."

If Recipient does not agree to incorporate significant comments from the review, Recipient will use the acknowledgment:

"The Framingham Heart Study is conducted and supported by the National Heart, Lung, and Blood Institute (NHLBI) in collaboration with Boston University. This manuscript was not prepared in collaboration with investigators of the Framingham Heart Study and does not necessarily reflect the opinions or views of the Framingham Heart Study, Boston University, or NHLBI."

7.3 Acknowledgments/Genetic Analysis Data. If Genetic Analysis Data are received, the Recipient agrees to acknowledge the contribution of Boston University staff (Framingham Heart Study) and/or the Investigator(s) who derived such data in any and all oral and written presentations, disclosures, and publications resulting from any and all analyses of such Genetic Analysis Data.

8. Non-Identification. Recipient agrees that Biological Material and Clinical Data will not be used, either alone or in conjunction with any other information in any effort whatsoever to establish the individual identities of any of the subjects from whom Clinical Data or Biological materials were obtained.

9. Use Limited to Research Project. Recipient agrees that Biological Material, its progeny, and unmodified or modified derivatives thereof will not be used in any experiments or procedures that are not disclosed and approved as part of the Research Project.

10. Use in Human Experimentation Prohibited. Recipient agrees that Biological Material, its progeny, and unmodified or modified derivatives thereof will not be used in human experimentation of any kind.

11. Compliance with Subjects' Informed Consent. Recipient agrees that Biological Material, its progeny, and unmodified or modified derivatives thereof will not be used for any purpose contrary to the subjects' applicable signed informed consent document(s). It is the responsibility of the Recipient's Principal Investigator to consult with the Framingham investigators and ascertain, specifically and in detail, the terms and conditions of applicable Framingham Study

informed consent documents.

12. No Distribution, Avoidance of Waste, Return of Materials. Recipient agrees to retain control over Clinical Data, Genetic Analysis Data and Biological Material, its progeny, and unmodified or modified derivatives thereof, and further agrees not to transfer Clinical Data, Genetic Analysis Data or Biological Material, its progeny, and unmodified or modified derivatives thereof, with or without charge, to any other entity or any individual. Recipient agrees, in handling the Biological Materials, to make reasonable efforts to avoid contamination or waste of the samples. When the Research Project is completed, or three (3) years have elapsed from the effective date of this Distribution Agreement, whichever occurs first, the Biological Material will be either returned to Boston University and NHLBI, or disposed of as mutually agreed upon by Boston University, NHLBI, and Recipient, unless an extension of this Agreement is obtained.

13. Recipient's Resulting Genetic Analysis Data to be Provided to NHLBI/Boston University. Recipient agrees to provide Boston University and NHLBI with a report every twelve (12) months during the term of this Agreement containing Genetic Analysis Data derived by Recipient, in the performance of the Research Project. Such report will cover all Genetic Analysis Data derived by Recipient up to six (6) months before the reporting date. Recipient agrees that Boston University and NHLBI may distribute these data to qualified scientific investigators requesting access through established NHLBI procedures and completing a signed Distribution Agreement comparable to this Agreement. Recipient will provide Genetic Analysis Data, indexed by genotyping ID number in the precise electronic format specified by NHLBI. When genotyping has been conducted, DNA marker names and allele sizes in numbers of base pairs will be provided for each individual subject as indexed by seven digit Framingham subject ID number; descriptive information about each typed marker that includes marker name, allele sizes in numbers of base pairs and corresponding frequencies, relative distances in Megabases and in Centimorgans, marker heterozygosity, and the source of information used to determine map location will also be provided. Recipient also agrees to submit all data relevant to the establishment of paternity at the time such determinations are made.

14. Costs/No Warranties. Cost for DNA distribution will be borne by the NHLBI at no cost to the recipient for quantities of DNA between 10ng to 10ug per sample, depending upon the needs of the study. Costs are subject to change following written notification from Boston University with the approval of NHLBI. NO WARRANTIES, EXPRESS OR IMPLIED, ARE OFFERED AS TO THE MERCHANTABILITY OR FITNESS FOR ANY PURPOSE OF THE BIOLOGICAL MATERIALS, GENETIC ANALYSIS DATA AND CLINICAL DATA PROVIDED TO RECIPIENT UNDER THIS AGREEMENT, OR THAT THE BIOLOGICAL MATERIALS, GENETIC ANALYSIS DATA OR CLINICAL DATA MAY BE EXPLOITED WITHOUT INFRINGING THE INTELLECTUAL PROPERTY OR PROPRIETARY RIGHTS OF ANY THIRD PARTIES.

15. Recipient's Responsibility for Handling Biological Materials. Recipient acknowledges that Biological Material has the potential for carrying viruses, latent viral genomes, and other infectious agents in an in apparent state. The Recipient agrees to treat Biological Material as if it were not free of contamination, and that Biological Material will be handled by trained persons under laboratory conditions that afford adequate biohazard containment. By accepting Biological

Material, Recipient assumes full responsibility for its safe and appropriate handling.

16. Non-Endorsement, Indemnification. Recipient agrees not to claim, infer, or imply Governmental endorsement of the Research Project, the entity, or personnel conducting the Research Project or any resulting commercial product(s) except as described in paragraph 7. To the extent permitted by law, Recipient agrees to hold the United States Government, Boston University, and all other investigator(s) who generated Genetic Analysis Data, and the agents and employees of each of them, harmless and to defend and indemnify all such parties for all liabilities, demands, damages, expenses, and losses arising out of Recipient's use for any purpose of Clinical Data, Genetic Analysis Data, and Biological Material, its byproducts, or modified or unmodified derivatives.

17. Accuracy of Data. Recipient agrees that the United States Government, Boston University, and the other investigator(s) who generated Genetic Analysis Data are not responsible for the accuracy of Genetic Analysis Data provided by other Recipients. The United States Government and Boston University are not responsible for the accuracy of Clinical Data or Biological Materials provided.

18. Recipient's Compliance with IRB Requirements. Recipient acknowledges that the conditions for use of this Biological Material have been approved by the Recipient's Institutional Review Board (IRB) in accordance with Department of Health and Human Services regulations at 45 CFR Part 46. Recipient agrees to comply fully with all such conditions and with the subjects' informed consent documents, and any additional conditions that may be imposed by the Boston University Medical Center Institutional Review Board (BUMC IRB). It is intended that the Recipient's agreements herein shall inure to the benefit of the research subjects, as well as to the parties to this agreement. Recipient agrees to report promptly to the BUMC IRB and the NHLBI any proposed change in the research project and any unanticipated problems involving risks to subjects or others. Recipient remains subject to applicable State and local laws and regulations and institutional policies which provide additional protections for human subjects.

19. Amendments. Amendments to this Distribution Agreement must be made in writing and signed by authorized representatives of both parties.

20. Termination. Boston University, in consultation with NHLBI, may terminate this Distribution Agreement if Recipient is in default of any condition of this Distribution Agreement and such default has not been remedied within 30 days after the date of written notice by Boston University of such default. Upon termination of this Distribution Agreement, Recipient agrees to return all unused Biological Materials and Clinical Data to Boston University.

21. Disqualification, Enforcement. Failure to comply with any of the terms specified herein may result in disqualification of Recipient from receiving additional Clinical Data, Biological Materials, and/or Genetic Analysis Data. The United States Government and/or Boston University shall have the right to institute and prosecute any proceeding at law or in equity against the Recipient for violating or threatening to violate the confidentiality requirements of this agreement, the limitations on the use of the data or materials provided, or both. Proceedings may be initiated against the violating party, or legal representatives, and assigns, for a restraining injunction, compensatory and punitive damages, mandamus, and/or any other proceeding in law

or equity, including obtaining the proceeds from any intellectual property or other rights that are derived in whole or in part from the breach of the confidentiality requirements or use limitations of this agreement. In addition, Recipient acknowledges and agrees that a breach or threatened breach of the confidentiality requirements or use limitations of this agreement may subject Recipient to legal action on the part of Framingham Study subjects, their families, or both.

22. Accurate Representations. Recipient expressly certifies that the contents of any statements made or reflected in this document are truthful and accurate.

23. Prior Distribution Agreements. The following two paragraphs apply only to Recipients that have entered into a previous Distribution Agreement:

23.1. Execution of this Distribution Agreement is contingent upon Recipient's compliance with all terms and conditions of existing Distribution Agreements with NHLBI, excluding the requirements stated in paragraph 4 of the previous Distribution Agreement.

23.2. If Recipient has executed a previous Distribution Agreement, Recipient agrees to provide Boston University and NHLBI with a report every twelve (12) months during the term of such prior Distribution Agreement containing Genetic Analysis Data derived by Recipient from any Clinical Data and Biological Materials previously received from Boston University. Such report will cover all Genetic Analysis Data derived by Recipient up to six (6) months before the reporting date. Recipient agrees that Boston University and NHLBI may distribute these data to qualified scientific investigators requesting access through established NHLBI procedures and completing a signed Distribution Agreement comparable to this Agreement. If the effective date of such previous Distribution Agreement was more than twelve (12) months before the time of the current request for Clinical Data and Biological Materials, and Recipient has not provided to Boston University Genetic Analysis Data derived from any Clinical Data and Biological Materials previously received from Boston University, Recipient agrees that provision to Boston University and NHLBI of such Genetic Analysis Data is a precondition for consideration of the current Distribution Agreement.

This Distribution Agreement is entered into as of :_____ (effective date)

RECIPIENT:

_____

Name of Recipient Entity:

_____

Name and Title of Recipient's Authorized Representative:

_____

_____

Signature and Date of Recipient's Authorized Representative:

_____

Date: _____

PRINCIPAL INVESTIGATOR:

Principal Investigator's Name and Title:

_____

Principal Investigator's Surface Mail Address:

_____

_____ _____

Principal Investigator's Email Address:

_____

Principal Investigator's Telephone Number:

_____

Principal Investigator's Fax Number:

_____

Signature and Date: Principal Investigator:

_____Date:_____

TRUSTEES OF BOSTON UNIVERSITY (BOSTON UNIVERSITY):

_____

Name and Title of Boston University's Authorized Representative:

_____

_____

Signature and Date of Boston University Authorized Representative:

_____

_____

Date:_____

NHLBI:

Name and Title of NHLBI's Authorized Representative:

_____ _____

Signature and Date of NHLBI Authorized Representative:

_____

Date: _____